Complete Summary

GUIDELINE TITLE

Radiotherapy for breast cancer in countries with limited resources: program implementation and evidence-based recommendations.

BIBLIOGRAPHIC SOURCE(S)

Bese NS, Kiel K, El-Gueddari Bel-K, Campbell OB, Awuah B, Vikram B, International Atomic Energy Agency. Radiotherapy for breast cancer in countries with limited resources: program implementation and evidence-based recommendations. Breast J 2006 Jan-Feb;12 Suppl 1:S96-102. [52 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nursing

Obstetrics and Gynecology
Oncology
Radiation Oncology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To review the resource requirements for implementing a radiotherapy program in the limited-resource setting, with special reference to treating breast cancer
- To discuss possible strategies for overcoming barriers to a radiotherapy program
- To provide evidence-based recommendations for radiotherapy for breast cancer in limited-resource settings

TARGET POPULATION

Women with breast cancer in limited-resource countries

INTERVENTIONS AND PRACTICES CONSIDERED

1. Whole-breast radiotherapy
2. Postmastectomy radiotherapy for early stage or locally advanced breast cancer
3. Palliative radiotherapy

MAJOR OUTCOMES CONSIDERED

- Disease-free survival
- Overall survival
- Local recurrence
- Distant metastasis
- Death
- Body image
- Quality of life
- Treatment time
- Treatment-related toxicity and morbidity
- Treatment safety and efficacy
- Level of breast cancer-related symptoms, including pathologic fractures, pain, discharge, and bleeding
- Level of function

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Consensus Statement Preparation

The observations from the 2002 Breast Health Global Initiative (BHGI) Global Summit (see companion document, "Breast Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines" in "Availability of Companion Documents" field) served as the basis of the 2005 BHGI Global Summit, where specific recommendations were addressed.

The BHGI guidelines were reexamined, revised, and extended at the 2005 BHGI Global Summit. Twelve national and international groups joined the BHGI as collaborating organizations (See Appendix A of the companion document, "Breast

Cancer in Limited-Resource Countries: An Overview of the Breast Health Global Initiative 2005 Guidelines"). In addition, to obtain input on international guideline development, the BHGI established affiliations with three World Health Organizations programs: the Cancer Control Programme, Health System Policies and Operations, and the Alliance for Health Policy and Systems Research. The 2005 Global Summit brought together more than 60 international experts from 33 countries of all resource levels. The experts had diverse specialties related to breast care and breast cancer: screening, pathology and cytology, surgery, oncology, radiation therapy, health economics, medical ethics, sociology, and advocacy. Each panel was charged with reviewing, updating, and extending the previously published guidelines on this topic and were asked to prepare a consensus statement summarizing the outcome of their work. See National Guideline Clearinghouse (NGC) summaries of the guidelines developed from these consensus statements: Breast cancer in limited-resource countries: early detection and access to care; Breast cancer in limited-resource countries: diagnosis and pathology; and Breast cancer in limited-resource countries: treatment and allocation of resources.

Individual Statement Preparation

Morning plenary speakers were invited to submit individual statements for publication on their topics along with the consensus statements. In many cases, individual statements were needed to develop and analyze specific topics that were too detailed and focused for inclusion in the consensus statements as a whole, but nonetheless were vital to an understanding of the overall guideline recommendations for limited-resource countries.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Published cost analyses were reviewed in the preparation of this guideline.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Individual Statement Selection and Review

In lieu of the standard external peer-review process, submitted individual statements underwent a special internal review process, reflecting the unique structure and goals of the Breast Health Global Initiative (BHGI) program. All individual statement submissions were reviewed by panel cochairs and selected internal BHGI nonauthor reviewers. Individual statements that did not address issues specific to limited-resource countries were referred for journal submission outside of the BHGI guidelines. Some individual statements that developed individual topics of a more limited scope relevant to limited-resource countries

were incorporated into guideline consensus articles. Individual statements that were accepted for publication were determined by the cochairs, internal BHGI reviewers, and the BHGI director to have specific merit in support of the consensus guidelines.

After final acceptance, all individual statements were coordinated with the consensus guideline statements for internal referencing as data in one or multiple consensus statements. The combination of consensus and individual statements represents a complete BHGI guideline compendium, which is the final work product of the 2005 Global Summit.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations for Radiotherapy for Breast Cancer

Radiotherapy has an important role in the treatment of breast cancer at every stage. In early stage disease, radiotherapy is an integral part of breast-conserving therapy. For patients with more advanced cancers, adjuvant radiotherapy substantially decreases the risk of local recurrence, and also improves the survival among patients with positive axillary lymph nodes. In locally advanced disease (often the most common presentation in the limited-resource setting), after neoadjuvant systemic therapy, patients require both radiotherapy and modified radical mastectomy in an effort to achieve local control. In addition, radiotherapy is a valuable tool for the palliation of distant metastasis such as bone and brain metastases, as well as palliation for local recurrences.

Delivery of radiotherapy for breast cancer in the doses needed and according to the schedules supported by current evidence (discussed subsequently and summarized in the table below) is essential for its effectiveness, as well as its safety. Ongoing studies are exploring the possibility of using lower doses or shorter schedules, which would reduce costs and workloads, but their use should be considered investigational at this time.

Breast cancer requires multimodality treatment that, in addition to radiotherapy, includes surgery and systemic therapy (chemotherapy, hormonal therapy, or both). Approaches for integrating these therapies for safe and effective breast cancer treatment in the limited-resource setting are given in an accompanying guideline. Here the guideline developers elaborate on delivery of radiotherapy in such settings by discussing the evidence base, doses and schedules, and issues such as sequencing with other therapies.

Recommended Doses and Schedules for Radiotherapy for Breast Cancer

Stage I or II breast cancer	Locally advanced breast cancer	Metastatic or recurrent breast cancer
Whole-breast radiotherapy • All patients: 50 Gy	• Patients who have a response to systemic therapy and can undergo breast-	• Patients with single symptomatic bone metastases: local-field radiotherapy

Stage I or II breast cancer	Locally advanced breast cancer	Metastatic or recurrent breast cancer
in 25 fractions over 5 weeks or 42.5 Gy in 16 fractions over 22 days, administered five times per week • Patients ≤50 years of age and patients with close surgical margins: an additional 16 Gy boost to the tumor bed <u>Postmastectomy radiotherapy</u> • Patients with positive axillary lymph nodes: 50 Gy in 25 fractions over 5 weeks, administered five times per week to the chest wall and supraclavicular area; the axilla is included only if axillary dissection was inadequate • Patients with negative axillary lymph nodes who have multiple adverse features (e.g., primary tumor larger than 2 cm, unsatisfactory surgical margins, lymphovascular invasion): 50 Gy in 25 fractions over 5 weeks, administered five times per week to the chest wall	conserving surgery: whole-breast radiotherapy • Patients who have a response to systemic therapy and require radical or modified radical mastectomy: postmastectomy radiotherapy • Patients whose tumors remain unresectable after two regimens of non-cross-resistant chemotherapy: whole-breast radiotherapy (including regional lymph nodes) followed, if possible, by mastectomy; if mastectomy is still not possible, then a further boost to the gross tumor using shrinking fields	with a single 8 Gy fraction • Patients with multiple symptomatic bone metastases: wide-field (e.g., hemibody) radiotherapy with 12 Gy in four fractions over 2 days, or—if preceded by intravenous ondansetron and dexamethasone—6 to 8 Gy in a single fraction • Patients with symptomatic brain metastases: steroids and whole-brain radiotherapy (30 Gy in 10 fractions or 20 Gy in 5 fractions); highly selected patients may benefit from craniotomy or radiosurgery • Patients with symptomatic soft tissue metastases: irradiation of the metastases • Patients with locally recurrent breast cancer after mastectomy: irradiation of the chest wall and regional lymph nodes, with a further boost to the gross tumor using shrinking fields

Whole-Breast Radiotherapy

Early stage (stage I or II) breast cancer is surgically treated by either excision of the cancer (lumpectomy) with negative margins or a mastectomy. Disease in the axilla is assessed by either axillary dissection or a sentinel node biopsy followed by axillary dissection if the sentinel node is positive. Radiotherapy is delivered to the breast in the case of breast-conserving surgery, or is delivered to the chest wall after mastectomy if axillary lymph nodes are involved or certain other adverse features are present (discussed in a later section).

Randomized trials have shown that there are no significant differences in disease-free or overall survival between patients treated by mastectomy and those treated by breast-conserving surgery and whole-breast radiotherapy. The main benefit of breast-conserving surgery and radiotherapy is preservation of body image and a better quality of life. Randomized studies evaluating the use of breast-conserving surgery plus adjuvant systemic treatment have demonstrated higher rates of local recurrence than after breast-conserving surgery plus radiotherapy and adjuvant systemic treatment, but major differences in survival have not been observed. In view of the higher rates of local recurrence, breast irradiation is currently recommended for most patients who undergo breast-conserving surgery. Breast-conserving surgery requires 1) high-quality breast imaging (mammography and ultrasound) and pathology services to ensure tumor free margins of excision, 2) surgeons experienced in achieving a good cosmetic result with negative pathologic margins of excision, and 3) radiotherapy facilities.

Radiotherapy should be started without a long delay after breast-conserving surgery because a prolonged postoperative interval may compromise local control. When chemotherapy is indicated, radiotherapy may follow chemotherapy, but for patients with close surgical margins, radiotherapy can be given first. In a prospective randomized trial, there were no significant differences in time to any event, distant metastasis, or death, whether radiotherapy or chemotherapy was given first. Concomitant chemoradiotherapy can reduce the overall treatment time, but the concomitant administration of anthracyclines should be avoided because of the risk of increased skin and cardiac morbidity. Regimens such as cyclophosphamide, methotrexate, fluorouracil (CMF) are cost effective and can be given concomitantly with irradiation. Radiation therapy should be completed without undue prolongation of the overall treatment time.

Most local relapses are observed in the vicinity of the primary tumor bed, and for this reason, partial breast irradiation is currently under investigation. The target volume is smaller; therefore the radiation can be accelerated and completed in only 1 week. However, robust long-term results and toxicity evaluations are not yet available. At present, after breast-conserving surgery, the target volume for irradiation should include the whole breast.

The most common schedule for irradiation used in clinical practice is 50 Gy in 25 fractions to the whole breast, administered daily, five times per week. In a large randomized trial, however, a shorter fractionation schedule (42.5 Gy in 16 fractions over 22 days) proved to be just as safe and effective. Other schedules (e.g., 40 Gy in 3 weeks) are currently under investigation. The shorter schedules permit more efficient use of resources, and thus more women can be treated with the existing equipment and personnel in countries with limited resources.

Evidence suggests that boost radiation to the lumpectomy site significantly improves the local control rate for women 50 years of age or younger. Therefore a 16 Gy additional radiation dose to the tumor bed is recommended for younger women, as well as for women with close surgical margins. The boost dose can be delivered by photons, electrons, or brachytherapy.

Postmastectomy Radiotherapy

Early Stage Breast Cancer

Total mastectomy remains an appropriate treatment for many patients with breast cancer in the developing world. Radiotherapy following mastectomy substantially improves local control. Local recurrence after mastectomy usually occurs within the first 12–24 months, even after adjuvant systemic therapy, most commonly in the chest wall, followed by the supraclavicular fossa. The major risk factor is positive axillary lymph nodes. Other risk factors are large tumor size, positive margins of resection, and lymphovascular invasion.

Studies have demonstrated that the use of postmastectomy irradiation improves overall survival in women with axillary lymph node-positive breast cancer. Postoperative radiotherapy to the chest wall and supraclavicular area is therefore recommended for all patients with four or more positive lymph nodes and should be considered for patients with one to three positive lymph nodes. Axillary irradiation is given only to those patients who did not undergo an adequate axillary dissection. Irradiation of the axilla is, in general, not recommended. The axillary and internal mammary regions are relatively uncommon sites of local recurrence (in comparison with the chest wall), while the morbidity from axillary irradiation (e.g., arm edema) or internal mammary irradiation (e.g., cardiac toxicity) is of concern. If sophisticated techniques of modern treatment planning and delivery are available, internal mammary irradiation is recommended for patients with clinically or pathologically positive internal mammary lymph nodes, and is considered for patients if the primary tumor is located at the inner quadrant with the other adverse risk factors. On the basis of a recent retrospective review, postoperative chest wall irradiation should also be considered for patients with negative axillary lymph nodes who have multiple adverse features (e.g., a primary tumor larger than 2 cm, unsatisfactory surgical margins, or lymphovascular invasion).

A regimen of 50 Gy in 5 weeks is widely used for postoperative irradiation, but more rapid fractionation regimens (e.g., 40 Gy in 3 weeks) are under investigation in randomized trials, some already completed. Such approaches, with appropriate quality control, may be particularly beneficial in countries with limited resources by reducing the radiotherapy workload and costs.

Information on the impact of the sequencing of postmastectomy radiotherapy and systemic chemotherapy on survival is limited. At present, radiotherapy is most commonly delivered after the completion of chemotherapy in patients with node-positive disease.

Locally Advanced Breast Cancer

In developing countries, a considerable proportion of the patients present with locally advanced breast cancer (LABC) that is inoperable due to direct extension to the ribs, intercostal muscles, or skin; edema (including peau d'orange) or ulceration of the skin of the breast; satellite skin nodules confined to the same breast; inflammatory carcinoma; metastases to the ipsilateral internal mammary lymph nodes; or metastases to the ipsilateral supraclavicular lymph nodes. Patients with LABC have a high probability of distant metastasis as well as a high probability of local recurrence. Initial treatment of LABC is systemic therapy. Approximately 80% of inoperable tumors treated with chemotherapy may regress sufficiently to become operable. Neoadjuvant hormonal therapy is beneficial in patients with hormone receptor-positive tumors. Following systemic therapy, most patients require a radical or modified radical mastectomy, followed by radiotherapy (selected noninflammatory breast cancers exhibiting a complete or partial clinical response to initial chemotherapy can be considered for breast-conserving surgery followed by radiotherapy). Unresectable tumors that remain unresectable even after two regimens of non– cross-resistant chemotherapy should be irradiated. This should be followed, whenever feasible, by mastectomy. If mastectomy is still not possible, then definitive radiotherapy can be applied, with a further boost to the gross tumor using shrinking fields.

Palliative Radiotherapy

In patients with metastatic breast cancer, radiotherapy is an effective tool for palliation of the symptoms. The goal is to prevent or relieve symptoms or loss of function for as long as possible. Patients with bone metastases comprise the largest group receiving palliative radiotherapy. Radiotherapy can prevent pathologic fractures in patients with lytic lesions in weight-bearing bones. Traditionally local field radiotherapy has been used for patients with symptomatic bone metastases. Evidence suggests that significant symptomatic relief can be obtained with a single 8 Gy fraction, a very cost-effective strategy. Wide-field radiotherapy (e.g., hemibody irradiation) can be used for patients with multiple bone metastases. The International Atomic Energy Agency (IAEA) conducted a multinational, prospective, randomized trial that showed that hemibody radiation of 12 Gy in four fractions delivered over 2 days was a suitable treatment regimen. Others have suggested that hemibody irradiation of 6–8 Gy in a single dose is also safe and effective, if preceded by intravenous ondansetron and dexamethasone.

Patients with brain metastases can survive for many months after radiotherapy. Whole-brain irradiation and steroids are recommended for alleviating symptoms from brain metastases. Selected patients with no extracranial disease who have one or few metastases and a good performance status can be treated with craniotomy or radiosurgery if available.

Palliative radiotherapy is also useful for patients with soft tissue metastases causing pain, discharge, or bleeding.

Locally recurrent breast cancer after mastectomy can occasionally be cured with radiotherapy to the chest wall and regional nodes. The likelihood of tumor control increases with a longer disease-free duration since the initial therapy and resection of the recurrent disease, and also depends on the number of sites involved.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of radiotherapy for treatment of breast cancer in countries with limited resources

POTENTIAL HARMS

- The axillary and internal mammary regions are relatively uncommon sites of local recurrence (in comparison with the chest wall), while the morbidity from axillary irradiation (e.g., arm edema) or internal mammary irradiation (e.g., cardiac toxicity) is of concern.
- Concomitant chemoradiotherapy can reduce the overall treatment time, but the concomitant administration of anthracyclines should be avoided because of the risk of increased skin and cardiac morbidity.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

See the original guideline document and companion document, "Breast Cancer in Limited-Resource Countries: Health Care Systems and Public Policy" (see "Availability of Companion Documents" field) for implementation strategies.

IMPLEMENTATION TOOLS

Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Bese NS, Kiel K, El-Gueddari Bel-K, Campbell OB, Awuah B, Vikram B, International Atomic Energy Agency. Radiotherapy for breast cancer in countries with limited resources: program implementation and evidence-based recommendations. Breast J 2006 Jan-Feb;12 Suppl 1:S96-102. [52 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Feb

GUIDELINE DEVELOPER(S)

Breast Health Global Initiative - Professional Association

SOURCE(S) OF FUNDING

Breast Health Global Initiative

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.

Print copies: Available from Bhadrasain Vikram, MD, Head, Section of Applied Radiation Biology and Radiotherapy, International Atomic Energy Agency, P.O. Box 100, Wagramer Strasse 5, A-1400 Vienna, Austria; E-mail: b.vikram@iaea.org

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Breast cancer in limited resource countries: an overview of the breast health global initiative 2005 guidelines. Breast J 2006 Jan-Feb;12 Suppl 1:S3-15. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.
- Breast cancer in limited-resource countries: health care systems and public policy. Breast J 2006 Jan-Feb;12 Suppl 1:S54-69. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Center Web site.

Print copies: Available from Benjamin O. Anderson, MD, Department of Surgery, Box 356410, University of Washington, Seattle, WA 98195, USA, or e-mail: banderso@u.washington.edu.

The following is also available:

- The Breast Health Global Initiative (BHGI) Resource-Stratified Matrix Guidelines. Available in Portable Document Format (PDF) from the Fred Hutchinson Cancer Research Web Site.

PATIENT RESOURCES

None available

NGC STATUS

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